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Prognostic factors for survival in stage IV rectal cancer: A Swedish nationwide case–control study

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ABSTRACT

Purpose: The aim was to identify patient-, tumor- and treatment-related prognostic factors for five-year survival in rectal cancer patients with synchronous stage IV disease.

Material and methods: This nationwide case-control study was based on the Swedish Colorectal Cancer Registry with supplementary information from medical records and the Swedish Inpatient Registry during the period 2000–2008. All resected rectal cancer patients with synchronous metastases that survived more than five years were included as cases. The control group consisted of corresponding patients who lived less than five years, matched in a 1:2 based on gender, age, resection of the rectal tumor, and the study period.

Results: A total of 405 patients were identified; 99 long-term survivors (LTS) and 182 short-term survivors (STS). Patient-related factors of symptoms and comorbidity did not differ between LTS and STS. Among the treatment-related factors, multiple site metastases ($p = 0.007$), bilobar liver metastasis ($p = 0.002$), and increasing number of liver metastasis ($p < 0.001$) were associated with STS. Prognostic treatment-related factors were pre-operative radiotherapy ($p = 0.001$), metastasectomy ($p < 0.001$), and radical resection of the primary tumor ($p = 0.014$). In the multivariable analysis, the single most important factor for becoming a LTS was a metastasectomy (hazard ratio: 8.474, 95% confidence interval: 4.098–17.543).

Conclusions: The most important prognostic factor for long-term survival in patients with stage IV rectal cancer was metastasectomy, especially liver surgery. With thorough selection of patients for metastasectomy more patients with metastasized rectal cancer may survive beyond five years.

1. Introduction

At the time of diagnosis, approximately 25% of rectal cancer patients present with synchronous metastatic disease [1] and the vast majority of metastases are located in the liver [2]. Most of these metastases are irresectable with reported resection rates of 5–15% [3,4]. Prognosis for stage IV disease is poor with a five-year survival rate of 3% [5]. However, five-year survival rates up to 58% have been reported in selected groups of patients in which liver surgery is performed [6,7].

Oncological and surgical treatments for stage IV rectal cancer patients have substantially changed in recent decades. The main changes in systemic oncological treatment were the introduction of oxaliplatin, irinotecan, and target therapies. In surgical treatment of metastases, there has been an increased resection rate of liver and lung metastases and also of peritoneal metastases. In liver surgery, there has been a shift towards the liver-first approach; i.e., resection of liver metastases after cycles of preoperative chemotherapy, followed by resection of the primary rectal tumor [8].

Several scoring systems based on prognostic factors have been suggested to predict survival after liver resection of colorectal liver metastases [9–11]. Because of changes in surgical and systemic oncological treatments over the years, and the inherent limitation of the scoring systems based on retrospective cohort studies, there is a need for further research in this evolving field to identify prognostic factors.

The aim of this nationwide registry-based case–control study of rectal cancer patients with synchronous stage IV disease was to identify patient-, tumor- and treatment-related prognostic factors for five-year survival.

Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; HR, hazard ratio; LTS, long-term survivors; STS, short-term survivors; RT, radiotherapy; SCRCR, Swedish Colorectal Cancer Registry

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2. Materials and methods

This case–control study was based on prospectively collected data from the Swedish Colorectal Cancer Registry (SCRCR) with clinical, surgical, pathological, and follow-up data. The registry covers more than 98% of diagnosed patients with adenocarcinoma in the rectum. Rectal adenocarcinoma was defined as a tumor with its lower border within 15 cm from the anal verge. A detailed description of the SCRCR has been reported previously [5].

Additional data on all patients was retrieved by scrutinizing medical records and gathering supplementary information from the Swedish Inpatient Registry on patients who underwent metastasectomy or ablative treatment of their metastases.

2.1. Study population

All rectal cancer patients from 2000 to 2008 with synchronous metastases who had survived more than five years were included and defined as long-term survivor cases (LTS). The control group, named the short-term survivor group (STS), consisted of corresponding patients (two per case) who lived less than five years, matched for gender, age, resection of the rectal tumor, and the study period. We defined synchronous and metachronous metastases as metastases diagnosed within and after three months from diagnosis of the primary rectal tumor, respectively.

A total of 405 patients were identified, including 135 cases and 270 controls (Fig. 1). After medical records were scrutinized, 36 cases were excluded because they had been misdiagnosed with stage IV when they in fact had a T4 rectal tumor without metastases or had metachronous metastases. Exclusion of a case resulted in exclusion of both controls, resulting in exclusion of 72 controls. An additional 16 controls were excluded for misdiagnosis, resulting in a study population of 99 cases and 182 controls.

2.2. Data variables

The SCRCR includes data on patient characteristics and details of treatment of the primary tumor. Variables not registered in the SCRCR were retrieved from medical records: i.e., American Society of Anesthesiologists (ASA) grading before 2007, comorbidity (cardiovascular disease, lung disease, diabetes, and cerebrovascular lesions), symptoms at the time of diagnosis (bowel obstruction, rectal bleeding, abdominal pain, change in stool habits, and anal pain), preoperative investigations, and metastatic burden (number, size, and localization) at the time of diagnosis, surgery of metastases, and pre- and postoperative oncological treatment. We used American Joint Committee on Cancer (AJCC) 6th edition for TNM classification.

According to Swedish national guidelines for rectal cancer treatment, the rectal tumor was categorized as “good”, “bad” and “ugly” [12]. During the investigated time-period, patients with “good” tumors did not receive any neoadjuvant therapy in addition to surgery. “Bad” tumors mostly received preoperative short-course radiotherapy (5 × 5Gy) with surgery within 4 days. Patients with “ugly” tumors underwent preoperative chemo-radiotherapy (50,4Gy that is 1,8Gy daily in 5 weeks). No patients were treated by the liver-first strategy during this time-period.

We obtained supplementary information from the Swedish Inpatient Registry regarding date, ablative treatment of metastases, and types of liver and lung resection. We defined metastasectomy as any surgical treatment on metastases (i.e., both ablative treatment and resection).

2.3. Statistical analysis

A conditional Cox regression analysis with a dummy variable for time was performed because the links between the cases and controls were retained. To avoid small variable sizes, the ASA scores were recoded into dichotomous variables (ASA1–2 versus ASA 3–4). The T-stage (T1–2 versus T3 versus T4) and N-stage (N0 versus N1–N2) scores were combined in a similar manner. Multiple conditional Cox regression analysis was performed, including all significant predictive variables from the univariable analyses. A p-value of < 0.05 was considered statistically significant. Data were analyzed using SPSS software (v. 24; IBM Corp., Armonk, NY, USA).

2.4. Ethics

The study was approved by the Regional Ethics Review Board in Uppsala and complied with the Declaration of Helsinki (Dnr 2011/079).

3. Results

3.1. Patient-related factors

There were no differences between LTS and STS regarding symptoms at diagnosis (i.e., changed bowel habits, rectal bleeding, bowel obstruction, abdominal pain, and anal pain), nor any differences in comorbidity with cardiovascular disease, lung disease, diabetes, or cerebrovascular lesions. In total, 87% of the patients were ASA 1–2, with no difference observed between the groups (Table 1).

3.2. Tumor-related factors

The distance of the rectal tumor from the anal verge and the T- and N-stages of the primary tumor did not differ between LTS and STS (Table 2). Metastatic lesions were located in the liver in 88%, lung in 14%, peritoneum in 2%, and other sites in 13%, of which 71.4% were distant lymph node metastases, with no significant difference observed between LTS and STS. Other locations of metastasis were gynecological organs (n = 4), skeleton (n = 5) and other parts of the abdomen (n = 4). Metastases at more than one site was seen in 8% of LTS and 20% of STS ($p = 0.006$). The median number of liver metastases was two for LTS and four for STS ($p < 0.001$) and unilobar liver engagement was more common in LTS (65%) than STS (36%) ($p = 0.002$) (Table 2). In patients with liver metastases, an increasing number of liver metastases was associated with increased risk of becoming STS ($p < 0.001$). In patients with more than five liver metastases, the risk of becoming STS increased fivefold (hazard ratio [HR]: 4.83, 95% confidence interval [CI]: 1.976–11.764, $p < 0.001$).

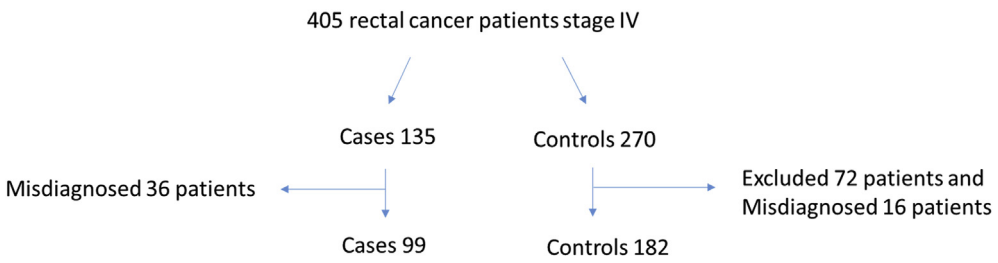

Fig. 1. Flowchart over cases and controls matched 1:2. Cases are long-term survivors and controls are short-term survivors.

Table 1
Patient-related factors for survival beyond five years in stage IV rectal cancer patients.

Patient-related factors	Long-term survival n = 99	Short-term survival n = 182	p-value
Age (years)	62 (29–83)	62 (27–83)	
Gender (male: female)	58:41	112:70	
Symptoms			
Changed bowel habits	53 (54)	97 (53)	0.757
Missing data	10 (10)	20 (11)	
Rectal bleeding	69 (70)	113 (62)	0.210
Missing data	10 (10)	20 (11)	
Bowel obstruction	4 (4)	6 (3)	0.643
Missing data	10 (10)	20 (11)	
Abdominal pain	16 (16)	27 (15)	0.730
Missing data	10 (10)	20 (11)	
Anal pain	12 (12)	15 (8)	0.595
Missing data	10 (10)	20 (11)	
Comorbidity			
Cardiovascular disease	32 (32)	49 (27)	0.280
Missing data	7 (7)	17 (9)	
Lung disease	8 (8)	9 (5)	0.248
Missing data	7 (7)	17 (9)	
Diabetes	5 (5)	17 (9)	0.089
Missing data	7 (7)	17 (9)	
Cerebrovascular lesions	2 (2)	5 (3)	0.725
Missing data	7 (7)	17 (9)	
ASA score			
I–II	39 (39)	65 (36)	0.290
III–IV	3 (3)	13 (7)	
Missing data	57 (58)	104 (57)	

Data expressed as n (%) unless expressed as median (range).
ASA, American Society of Anesthesiologists.

3.3. Treatment-related factors

Preoperative radiotherapy (RT) was given more often in LTS (67.7%) than STS (47.8%) ($p < 0.001$; Table 3). The type of primary tumor resection did not differ between LTS and STS. Local radical resection of the primary tumor was performed in 86% of LTS and 73% of STS ($p = 0.014$; Table 3). Anastomotic leakage was detected in 29 of the 160 patients (18%) with anterior resection, with no difference between the groups. Relaparotomy was performed in 18% of the STS and 14% of the LTS ($p = 0.572$).

One hundred thirty-nine metastasectomies were performed in 123 patients (44%), and these were more common in LTS (78%) than STS (25%) ($p < 0.001$; Table 3). Liver resection was performed in 70% versus 40% and lung resection in 19% versus 3% of LTS and STS, respectively, although no significant differences were seen between the groups. Lymph gland resection was performed in two patients (1.5%), resection of peritoneal carcinomatosis in two patients (1.5%), and resection of gynecological organs in two patients (1.5%). In 21 patients (8.5% of all patients with liver metastases), a simultaneous resection of the rectal tumor and the liver metastases was performed; thirteen of these were LTS and eight were STS ($p = 0.013$). None of the patients had resection of their metastases before surgery of the primary tumor. Only a few patients received multiple metastasectomies.

Twenty-two of the 99 LTS did not undergo surgical treatment for their metastases (details described in Table 4). One-third of these patients had more metastases in locations other than liver and lung. The median number of liver metastases was three times greater in the group that did not undergo metastasectomy.

Table 2
Tumor-related factors (primary tumor and metastatic burden) for survival beyond five years in stage IV rectal cancer patients.

	Long-term survivors n = 99	Short-term survivors n = 182	p-value
Tumor distance to anal verge (cm)	9 (0–15)	10 (0–15)	0.210
Missing data	0	3	
T-stage			0.293
1–2	11 (11)	10 (5.5)	
3	62 (63)	127 (70)	
4	15 (15)	24 (13)	
Missing data	11 (11)	21 (11.5)	
N-stage			0.094
0	27 (27)	34 (19)	
1–2	58 (58)	119 (65)	
Missing data	14 (14)	29 (16)	
Metastases localization[a]			
Liver	84 (85)	162 (89)	0.332
Missing data	0 (0)	1 (1)	
Lung	11 (11)	29 (16)	0.155
Missing data	0 (0)	1 (1)	
Peritoneum	0 (0)	6 (3)	0.290
Missing data	0 (0)	1 (1)	
Other	13 (13)	22 (12)	0.951
Missing data	0 (0)	1 (1)	
Metastases localization			0.007*
One site	91 (92)	144 (79)	
Multiple sites	8 (8)	37 (20)	
Missing data	0 (0)	1 (1)	
Number of liver metastases[b]	2 (1–10)	4 (1–10)	< 0.001*
Missing data	9	27	
Liver lobe localization of metastases[b]			0.002*
Unilobar	54 (65)	58 (36)	
Bilobar	18 (21)	81 (50)	
Missing data	12 (14)	23 (14)	

Data expressed as n (%) unless expressed as median (range).
[a] Patients can have metastasis in multiple organs.
[b] Presented data is based only on patients with liver metastases (long-term survival with liver metastases = 84 and short-term survival with liver metastases = 162).

3.4. Multiple conditional Cox regression analysis of prognostic factors

The multivariable analysis (Table 5) including all patients showed that the single most important factor for becoming an LTS was metastasectomy (HR: 8.264, 95% CI: 3.984–16.949). However, when metastasectomy as a factor was excluded, preoperative RT (HR: 2.433, 95% CI: 1.345–4.404) was an important factor for becoming an LTS.

4. Discussion

This nationwide case–control study based on prospectively collected data of rectal cancer patients with synchronous metastases and aimed at identifying patient-, tumor- and treatment-related prognostic factors that were important for five-year survival. The most important factor for survival was shown to be surgical treatment of the metastases. Preoperative RT was also found to be an important prognostic factor for LTS.

The case–control design of the present study resulted in comparable groups regarding study period, age, gender, comorbidities, and systemic oncological treatments. The liver was the most frequent site of metastases in both LTS and STS patients. The LTS patients had fewer liver metastases and less multisite metastases, and unilobar liver engagement was more common in those living more than five years.

Table 3
Treatment-related factors (treatment of primary tumor and metastases) for survival beyond five years in stage IV rectal cancer patients.

	Long-term survivors n = 99	Short-term survivors n = 182	p-value
Preoperative radiotherapy[a]	67 (68)	87 (48)	0.001*
Missing data	0 (0)	0 (0)	
Preoperative chemotherapy[a]	14 (14)	24 (13)	0.551
Missing data	6 (6)	18 (10)	
Bowel resection			0.856
Anterior resection	55 (56)	105 (58)	
Abdominoperineal excision	21 (21)	38 (21)	
Hartmann's operation	23 (23)	39 (21)	
Radical primary resection (R0)	85 (86)	133 (73)	0.014*
Missing data	1 (1)	2 (1)	
Metastasectomy	77 (78)	46 (25)	< 0.001*
Missing data	0 (0)	0 (0)	
Postoperative chemotherapy[a]	69 (70)	120 (66)	0.558
Missing data	14 (14)	32 (18)	

Data expressed as n (%) unless expressed as median (range).
[a] Pre- and postoperative treatments are in relation to the primary tumor resection.

Table 4
Characteristics of long-term survivors without metastasectomy in stage IV rectal cancer patients.

	LTS, no metastasectomy (n = 22)	LTS with metastasectomy (n = 77)	p-value
Metastatic burden			
Localization[b]			
Liver	14 (64)	70 (91)	0.004*
Missing data	0 (0)	0 (0)	
Lung	3 (14)	8 (10)	0.704
Missing data	0 (0)	0 (0)	
Other	7 (32)	6 (8)	0.008*
Missing data	0 (0)	0 (0)	
Metastases localization			1.000
One site	20 (91)	71 (92)	
Multiples site	2 (9)	6 (8)	
Missing data	0 (0)	0 (0)	
Number of liver metastases	3.5 (1–10)	1 (1–10)	0.002*
Missing data	4 (18)	5 (6)	
Localization of liver metastases[c]			0.108
Unilobar	5 (36)	49 (70)	
Bilobar	5 (36)	13 (19)	
Missing data	4 (28)	8 (11)	
Treatment-related factors			
Preoperative radiotherapy[a]	9 (41)	58 (75)	0.004*
Missing data	0 (0)	0 (0)	
Preoperative chemotherapy[a]	1 (5)	13 (17)	0.290
Missing data	4 (18)	2 (3)	
Radical primary resection	17 (77)	68 (88)	0.159
Missing data	0 (0)	1 (2)	
Postoperative chemotherapy[a]	12 (54)	57 (74)	1.000
Missing data	7 (32)	7 (9)	

Data expressed as n (%) unless expressed as median (range).
[a] Pre- and postoperative treatments are in relation to the primary tumor resection.
[b] Patients can have metastasis in multiple organsD.
[c] Only those with liver metastases are presented; i.e., long-term survival with liver metastases who underwent metastasectomy (n = 70) and long-term survival with liver metastases who did not undergo metastasectomy (n = 14).

Previous studies have shown that prognostic factors of survival after metastasectomy of colorectal liver metastases include maximum size of the liver metastases [6,10,11,13–17], number of liver metastases [6,10,11,13–16,18–25], and distribution of liver metastases [13,14,26]. However, there are contradictions in the literature regarding these factors, probably due to different study periods and changes in oncological and surgical treatments over the years. Different studies also have different endpoints, exclusion criteria, and study populations. There are also contradictions in the literature on whether primary tumor-related factors are related to survival after metastasectomy of colorectal liver metastases. In this study, tumor-related prognostic factors such as T- and N-stages and tumor distance from the anal verge were not related to LTS, which is consistent with some studies [13,17,18,22,25–27]. However, other studies have found primary tumor stage [11,15] and node status [6,7,10,11,14–16,20,21,23–25] to be prognostic factors of survival after metastasectomy of colorectal liver metastases, which could be explained by patient selection and changes in tumor classification over time.

We included all rectal cancer patients in Sweden with synchronous metastases at diagnosis that survived more than five years. This corresponds to approximately 10 patients a year, with a yearly prevalence of 3.7% among patients with synchronous metastases. Most of these patients had liver metastases and most metastasectomies were confined to the liver. Surprisingly few patients with synchronous metastases surviving more than five years were found in the registry despite the improvements in oncological and surgical quality in recent decades. In a highly selective group of patients with synchronous and metachronous disease, five-year survival rates up to 58% and 68% have been reported after liver and lung metastasectomy, respectively [6,7,28].

An important question is whether patients with metastatic rectal cancer that survived for more than five years sought medical health care at an earlier stage due to symptoms from either the metastases or the primary tumor. However, we could not find any differences between LTS and STS and both groups presented with rectal bleeding and changes in bowel habits as the most frequent symptoms.

In the multiple regression analysis, metastasectomy was the most important factor for becoming LTS, but a minority of the LTS had no surgery for the metastases. Some advocate that patients with small pulmonary metastases may become LTS without metastasectomy; however, this could not be supported in our data. One can also speculate that these 22 patients became LTS through misdiagnosis. The diagnostic imaging performed might have shown signs of metastases, or metastastatic disease may have been suspected during surgery, but these findings might have been benign tumors or cysts.

Our study has the inherent limitation of retrospective studies based on national registries. Retrieving medical journals from all surgical departments in Sweden was challenging and still resulted in missing data. However, the medical journals complemented and strengthened the validity of the analyzed data from the SCRCR and the Swedish Inpatient Registry. Other limitations of this study were the lack of

Table 5
Multiple conditional Cox regression analysis of prognostic factors in stage IV rectal cancer patients who survive d beyond five years.

	Prognostic factors for long-term survival			Prognostic factors for long-term survival excluding metastasectomy		
	HR	95% CI	p-value	HR	95% CI	p-value
Metastasectomy	8.264	3.984–16.949	< 0.001*			
Preoperative radiotherapy	1.522	0.743–3.115	0.251	2.433	1.345–4.405	0.003*
Radical primary resection	1.351	0.556–3.283	0.507	2.123	0.986–4.573	0.054
More than one site metastasis	0.422	0.131–1.361	0.149	0.400	0.147–1.090	0.073

The reference is the controls (short-term survivors). HR, hazard ratio; CI, confidence interval.

information on mutation status of the primary tumor and that the different oncological treatments could not be assessed. Nonetheless, the case–control design resulted in a homogenous and comparable group of patients with rectal cancer. Furthermore, most studies on prognostic factors in patients with metastases have a case mixture including both colonic and rectal cancer patients, which results in an inhomogeneous cohort, whereas this study included only patients with rectal cancer. Notably, the patient cohort was from 2000 to 2008; therefore, most patients had their metastasectomies performed after resection of the primary tumor while few had simultaneous operations and none were treated by the liver-first strategy, which is more common practice today.

5. Conclusion

The most important prognostic factor for long-term survival in patients with stage IV rectal cancer was metastasectomy, especially liver surgery, regardless of patient-related factors. All rectal cancer patients with metastases should be discussed at multidisciplinary meetings, and with thorough selection of patients for metastasectomy more patients with metastasized rectal cancer may survive beyond five years.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.04.005.

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